

**Position Paper Regarding FDA - Sponsored Joint Public
Meeting of Levothyroxine Sodium Products, Washington DC,
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Bruce D Weintraub, MD
Chief Operating Officer
Chief Scientific Officer
Trophogen, Inc
6 Taft Court, Suite 150
Rockville, MD 20850
phone: 301-838-1935 x 102
fax: 301-762-6287
e-mail: bweintraub@trophogen.com

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Disclosure of Potential Conflicts of Interest

I have been a paid consultant for the last two months to Sandoz, strongly supporting its position on generic L- thyroxine preparations. However, for the previous 20 years I had been intermittently a paid consultant to various companies manufacturing the brand name L-thyroxine preparation, Synthroid, including Flint, Boots and Knoll, but not Abbott. Thus I feel I have a balanced record of consultant experiences to both brand name and generic manufacturers and believe that this position paper is unbiased and reflects my current sincerely-held beliefs.

Background, Qualifications, Publications and Awards

For more than 30 years I have been an academic professor, lab chief and clinical thyroidologist at Harvard, NIH and University of Maryland, focusing my research efforts on pituitary and recombinant TSH as well as thyroid clinical disorders and thyroid hormone action. I am also the co-inventor and a leading investigator in the development of recombinant TSH, approved by the FDA in 1998 for the diagnosis of thyroid cancer. During the development of this drug I became very familiar with FDA standards for drug development and for bioequivalence.

For the last 4 years I have been a co-founder, Chief Operating Officer and Chief Scientific Officer of a biotech company, Trophogen, Inc. My private sector drug development experience complements my academic drug development experience particularly relating to FDA standards.

I have published over 245 original papers and 45 book chapters including several leading thyroid textbooks. I have also received many international awards for my research and for the development of recombinant TSH. Representative publications

and awards particularly relevant for the current position paper are as follows:

Representative Publications:

Staub, J.-J., Althaus, B. U., Engler, H., Ryff, A. S., Trabucco, P., Marquardt, K., Burckhardt, D., Girard, J., and *Weintraub, B. D.*: Spectrum of subclinical and overt hypothyroidism: Effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. Amer. J. Med. 92:631-642, 1992.

Gorden, P., and *Weintraub, B. D.*: Radioreceptor and other functional hormone assays. In Wilson, J. D., and Foster, D. F. (eds.), Williams' Textbook of Endocrinology, 8th Edition. W. B. Saunders, Philadelphia, 1992, pp. 1647-1661.

Najjar, S. M., and *Weintraub, B. D.*: Radioimmunoassay and radioreceptorassay: past, present and future. In dePablo, F. Scanes, C., & *Weintraub, B. D.* (eds.), Techniques in Endocrine Research. Academic Press, San Diego, 1993, pp. 3-23.

Wondisford, F. E., Meier, C. A., and *Weintraub, B. D.*: Thyroid-stimulating hormone in health and disease. In DeGroot, L. J. (ed.), Endocrinology, 3rd Edition. W.B. Saunders Company, Orlando, 1993, Vol. 1, pp. 208-217.

Weintraub, B. D., Kim, M. D., Bodenner, D. L., Thotakura, N. R., Szkudlinski, M. W., Joshi, L., & Murata, Y.: Regulation and expression of thyroid-stimulating hormone. In Lustbader, J. W., Puett, J. D., and Ruddon, R. (eds.), Glycoprotein Hormones: Structure, Function & Clinical Implications. Springer Verlag, New York, 1993, pp. 75-78

Weintraub, B. D.: Diverse mechanisms for regulation of hormone synthesis and action: Relationship to endocrine diseases and the human genome project. In *Weintraub, B.D.* (ed.), Molecular Endocrinology: Basic Concepts and Clinical Correlations. Raven Press, New York, 1994, pp. 1-11.

Wondisford, F. E., Magner, J. A., and *Weintraub, B. D.*: Chemistry and biosynthesis of thyrotropin. In Braverman, L. E., and Utiger, R. D. (eds.), Werner and Ingbar's The Thyroid, 7th Edition. Lippincott-Raven Publishers, Philadelphia, 1996, pp. 190-207.

Cohen, R., *Weintraub, B. D.*, and Wondisford, F.E.: Chemistry and Biosynthesis of Thyrotropin. In Braverman, L. E., and Utiger, R. D. (eds.), Werner and Ingbar's The Thyroid, 8th Edition. Lippincott-Raven Publishers, Philadelphia, 2000, pp. 202-219.

Weintraub, B. D., Kazlauskaitė, R., Grossmann, M., and Szkudlinski, M. Thyroid-stimulating hormone and regulation of the thyroid axis. In DeGroot, L. J. and Jameson, JL(eds.), Endocrinology, 4th Edition. W.B. Saunders Company, Orlando, 2001, pp 1345-1360.

Szkudlinski, M., Kazlauskaitė, R. and *Weintraub, B. D.* Thyroid-stimulating hormone and regulation of the thyroid axis. In DeGroot, L. J. and Jameson, JL(eds.), Endocrinology, 5th Edition. W.B. Saunders Company, Orlando, 2005, in press.

Representative Awards:

- 1979 Van Meter-Armour Prize of American Thyroid Association
- 1981 Ernst Oppenheimer Memorial Award of The Endocrine Society
- 1992 Sidney Ingbar Memorial Award of Harvard Medical School & the Beth Israel Hospital
- 1992 Commendation Medal of the United States Public Health Service
- 1994 Meritorious Service Medal of the United States Public Health Service
- 1994 Sidney Ingbar Award of the American Thyroid Association
- 1995 Lawson Wilkens Society Award
- 1997 Knoll Mentorship Award of the Endocrine Society
- 2002 Light of Life Award of Memorial Sloan Kettering Cancer Center

T4 or free T4 is the direct and accurately measured analyte and is the most meaningful chemical measure of drug absorption and bioequivalence using conventional FDA standards

I strongly support the position of the FDA and of the generic L-thyroxine manufacturers that bioequivalence studies for L-thyroxine should use the conventional direct measurement of the analyte T4 or free T4. This analyte is highly soluble and very easy to measure with great accuracy. It is more appropriate for bioequivalency studies than any indirect measurement of thyroid hormone action, even a very sensitive one like TSH (see below). The FDA's standards of direct measurement of the analyte for bioequivalence, wherever possible, have stood the test of time even for drugs with narrow therapeutic/ toxic ratios. There is no compelling evidence that the FDA should modify its time-honored standards for bioequivalence solely for L-thyroxine other than a strong bias and dogmatic beliefs of certain clinicians based solely on retrospective studies without proper controls (see 2 such studies critiqued below). Convincing evidence to challenge the FDA's well-accepted and conventional standards of bioequivalency solely for L-thyroxine would require a well-designed prospective study with proper controls of mock T4 preparation switching and with careful monitoring by the FDA to assure objectivity, freedom from bias and possible conflicts of interest (see below).

The selection of a clinical and analytic measure to test bioequivalence must meet statistical thresholds of consistency and control. Moreover, bioequivalence is also a test of product chemistry with the chemical's efficacy already established through innovator clinical trials. Finally, the confidence in any bioequivalence rating is dependent upon the consistency in the application of in vivo direct drug presence measurements. All of the above standard bioequivalence criteria for L-thyroxine preparations are met fully by direct measurement of T4.

Proposed Use of TSH Measurement to Supplement or Replace the Use of Direct T4 Measurements in L-Thyroxine Bioequivalency Studies

Based on the currently available scientific evidence I do not believe that FDA should change its well-established standards of direct T4 measurements and use TSH measurement as either a supplement or as a replacement in L-thyroxine bioequivalency testing.

Although TSH is usually a very sensitive measure of thyroid function it is still an indirect measure and thus has several limitations whereby it can be affected by factors other than serum T4 levels. Several of these factors are well recognized by clinicians and include:

Diurnal variation

Non-thyroid illness

Central (pituitary or hypothalamic) hypothyroidism

Psychotropic drugs

Heterophilic antibodies

In fact the hypothyroidism associated with these conditions is successfully controlled using T4 or freeT4 monitoring in place of TSH. Moreover, TSH is also an invalid drug bioequivalence measure as a result of relatively high intra-patient variations (within each individual patient) that preclude accurate or meaningful statistical analysis of drug presence across a test population.

Critique of Two Studies Cited by Proponents of Use of TSH Testing for Bioequivalence

Among several retrospective and potentially biased studies cited by the proponents of TSH testing for L-thyroxine bioequivalence, two studies were particularly emphasized. The first of these was by Carr et al. Clin Endocrinol 1988; 28:325-333. Although this study showed the very high sensitivity of TSH measurement for detecting 25 ug incremental changes in T4 administration, it did not directly address the bioequivalence issue currently being considered. First, there is no evidence that 25 ug increments in T4 dose would not also be detected clearly by direct measurement of T4, given the great precision of its measurement and its freedom from indirect factors affecting TSH as cited above. Secondly, the metabolic and clinical impact of changes in TSH levels, especially within the normal range, were not studied in this paper. Many other studies only show convincing metabolic and clinical impact when TSH levels are well above or below the normal range for long periods of time (see discussion below of "sub clinical" hypo- or hyperthyroidism). Such changes should, again, be readily detected by the precision and directness of T4 testing in bioequivalence studies.

A second study emphasized by proponents of the use of TSH in bioequivalence testing was the Pharmetrics study of insurance claims database of 50 managed healthcare plans. This study was not published and not peer reviewed and apparently was funded by a brand name L-thyroxine manufacturer, and thus suffers from potential bias (see below for discussion of potential bias and conflicts of interest). Nonetheless, the results of this study are interesting. Rather than supporting the position that there is a problem in L-thyroxine preparation switching using the current FDA bioequivalence methods, the study shows quite the opposite. In this study the average TSH value before switching was 2.39 and after switching it was 3.32. Firstly, there was no control of a

mock switch keeping patients on the same L-thyroxine preparation to determine the baseline variability of TSH with time which in my clinical experience is considerable and I feel could fully explain these results. Secondly, even if some of the change in TSH values was accounted for by real changes in the L-thyroxine preparations, I do not believe there would be any clinical or metabolic significance of such a small change within the normal range of TSH. Finally, even for the minority of patients cited who may have had a change of > 2.0 , I do not believe that this would have clinical or metabolic impact. This is true especially if physicians follow practice guidelines to recheck TSH levels at least twice yearly. Thus even without proof of metabolic impact a physician could readily re-titrate the L-thyroxine dose to any level of TSH desired, and such intermittent re-titration is currently required of patients even on the same preparation because of variability in compliance, weight and dietary changes, pregnancy and a host of other known and unknown factors.

Any proposed future studies of T4 switching must be much more rigorously designed than the Pharmetrics study, and clinical anecdotes such as presented frequently at the May 23 meeting are not at all acceptable for making FDA policy decisions. A properly designed L-thyroxine preparation switching study must be prospective, randomized, analyzed blindly and must contain a mock switch control as described above. It should also be closely monitored by the FDA to assure objectivity and freedom from bias and be published to assure rigorous peer review.

Importance of Generic Preparations of L-Thyroxine

At the May 23 meeting many physicians cited anecdotal evidence of a problem in the use of generic L-thyroxine preparations. Evidence for physician surveys reporting results against use of generics was also presented. However, those surveys suffered from bias in that the questions were posed in way reflecting the

negative views of survey organizers and many were clearly leading questions.

Such a bias against use of newly introduced generics is common in all therapeutic fields and tends to decline with more experience and a continuing record of generic drug safety (see below). First, physicians may feel a loss of control when generics may be substituted for their prescribed name brand preparations. Second, patients may be confused and even alarmed by preparation switching if physicians and pharmacists have not taken the time to explain the rationale for this to them in advance. Of course patients will become biased against generics if their physicians communicate their own bias to them.

Despite this potential bias of physicians and patients against newly introduced generics, the FDA has a responsibility to the public, the Congress and the entire health care industry to develop bioequivalent generics. In the case of L-thyroxine preparations, the FDA has fulfilled its responsibility laudably. Never before in the long history of L-thyroxine therapy have such rigorous standards of bioequivalence been established by FDA. It is unfortunate that this fundamental and important point seems to have been lost in the heated debates of May 23.

The existence of generics is based on careful legislative balancing of competing industry viewpoints in which Congress elected to create a new pathway to achieve a diverse array of social values and policy objectives. The Hatch-Waxman Act puts both the Congressional and FDA seals of approval on the generic products through a rigorous process of development, submission, filing, review, and approval. Moreover, the cost of a single TSH test to monitor a therapy change is dwarfed by the years of savings in utilizing FDA-rated bioequivalent generic products. The costs of the routine clinical monitoring of responses to a therapeutic change are outweighed by the benefit of **life-long**

therapeutic maintenance using a bioequivalent generic product in place of a premium-priced brand product. Using bioequivalent generics for chronic care therapies clearly reduces the burden of these therapies across the healthcare continuum. Finally, cost reduction of older therapies allows greater access to breakthrough therapies by releasing resources that might otherwise have funded a brand label with a clinical value equal to the bioequivalent generics.

Patient Safety Issues in Use of Generics

I feel that current FDA bioequivalence standards are so rigorous that there are absolutely no patient safety issues related to the switching of L-thyroxine preparations. Moreover, as mentioned above, current standards of care call for routine lab value monitoring (TSH with or without T4 or free T4) at least once or twice yearly. Such monitoring provides adequate safeguards to prevent any chronic over or under treatment and greatly mitigates any threat of long-term health risks from exogenously-induced hyper-or hypo-thyroidism

Consensus views of thyroidologists relating to the clinical significance of so-called "subclinical" hypo- or hyperthyroidism (decreased or increased TSH with normal T4 or free T4) are associated with TSH values well above or below the normal range for periods of many years or even decades; such extreme TSH values for such long periods would not be encountered in patients switched to generics and receiving recommended monitoring. The Pharmetrics study cited above, despite its many described limitations and potential for bias, clearly demonstrates this point. Thus, there is no convincing evidence for claims of such a narrow therapeutic range for L-thyroxine therapy that would make current FDA bioequivalence standards inadequate. In any case, such claims would have to take into account the **duration of such therapy**.

The most important factor relating to patient safety is the nearly perfect safety record of generic L-thyroxine preparations since their introduction described below. Untoward events of any kind have been low, and quite comparable to that expected for a placebo control group.

As of April 28, 2005

Tablets Released	~1,300,000,000
Prescriptions @ 30 tablets each	~43,000,000
Adverse Events Reported	68
Serious Events	0

Potential for Conflicts of Interest and Bias

At the May 23 meeting an audience questioner accused certain panelists of having conflicts of interest because they and the American Thyroid Association have been heavily supported by brand name manufacturers of L-thyroxine over many years. I felt the response of the panelist was inadequate to address this important issue. The response was argumentative and guarded. It should have dealt with this admittedly sensitive issue in a much more candid and forthright manner. That panelist and others providing verbal and written testimony should openly disclose all potential conflicts of interest of individuals or of the Association because of past or current support by brand name manufacturers of L-thyroxine, as I have done in this current position paper. The American Thyroid Association is a highly noble and ethical organization and I am proud to be a member. Similarly, all its members are the most expert thyroidologists in the country and are motivated totally by their concerns for patient well being.

Nonetheless, this past record of heavy funding primarily by brand name manufacturers of L-thyroxine creates at least the appearance of conflicts of interest and requires full disclosure by all. The FDA must take such potential conflicts of interest and bias into account in evaluating all testimony and in evaluating the results of certain studies supported by brand name manufacturers of L-thyroxine. To obviate this problem the FDA should be directly involved to monitor future studies of L-thyroxine switching for objectivity, especially if these studies are supported by manufacturers of brand name products.

Summary

I fully support the current well-established and time-tested FDA standards for direct measurement of T4 for establishing bioequivalency of L-thyroxine preparations. I find no compelling evidence that bioequivalence standards would be enhanced by adding the measurement of TSH. Generic preparations of L-thyroxine are important new therapeutics for thyroid patients and the FDA should be lauded for developing and approving these products using such rigorous methodology. I do not believe generics or preparation switching pose any patient safety issues especially if clinical care guidelines for regular TSH monitoring are followed. There are potential conflicts of interest for those giving testimony in this field which should be addressed by the FDA by requiring full disclosures and by direct FDA involvement in monitoring future studies of L-thyroxine preparation switching.